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Establishing the Transitory Existence of Amorphous Phases in Crystallization Pathways by the CLASSIC NMR Technique

Colan E. Hughes, P. Andrew Williams, Benson M. Kariuki and Kenneth D. M. Harris*[a]

Abstract: With the growing realization that crystallization processes may evolve through a sequence of different solid forms, including amorphous precursor phases, the development of suitable *in-situ* experimental probes is essential for comprehensively mapping the time-evolution of such processes. Here we demonstrate that the CLASSIC NMR (Combined Liquid- And Solid-State *In-situ* Crystallization NMR) strategy is a powerful technique for revealing the transitory existence of amorphous phases during crystallization processes, applying this technique to study crystallization of DL-menthol and L-menthol from their molten liquid phases. The CLASSIC NMR results provide direct insights into the conditions (including the specific time period) under which the molten liquid phase, transitory amorphous phases and final crystalline phases exist during these crystallization processes.

It is now widely believed that amorphous phases can play an important role as transitory intermediates in crystallization processes.[1] A prominent example is calcium carbonate, for which an amorphous phase has been reported as the precursor to various crystalline polymorphs, both *in vivo*[2] and *in vitro*.[3] Intermediate amorphous phases also arise during crystallization of organic materials, including the pharmaceuticals ibuprofen[4] and paracetamol.[5] As non-classical theories of crystal nucleation[6] often invoke amorphous phases as precursors to crystalline products,[1a] suitable *in-situ* techniques[7] that allow the identification and characterization of *all* solid phases present as a function of time during crystallization offer the prospect to test such theories through rigorous experimental investigation, revealing intermediate solid forms that are too unstable or too short-lived to be isolated for *ex-situ* characterization

NMR is very suitable for such *in-situ* studies because solid-state NMR is able to readily distinguish and identify different crystalline forms[8] (e.g., polymorphs, solvates, co-crystals) and amorphous phases,[9] and because liquid-state NMR is able to characterize the liquid phase in crystallization systems. In general, the experimental methods used to measure solid-state NMR spectra and liquid-state NMR spectra are different, which is exploited in the CLASSIC NMR (Combined Liquid- And Solid-State *In-situ* Crystallization NMR) strategy.[10] The basis of CLASSIC NMR is to apply two different pulse sequences alternately during *in-situ* NMR studies of crystallization, with one pulse sequence selectively measuring the liquid-state NMR spectrum and the other pulse sequence selectively measuring the solid-state NMR spectrum, revealing complementary information on the evolution of *both* the liquid phase *and* the solid phase as a function of time during crystallization. A range of crystallization processes have been studied[10,11] by the CLASSIC NMR strategy, as well as by *in-situ* studies involving only solid-state NMR measurements, revealing the occurrence of polymorphic transformations during crystallization[11a,11b] and the discovery of new crystalline phases as intermediates on crystallization pathways.[11c] Co-crystal formation by solution-state crystallization[11c,11f] and by solid-state transformations[11d] have also been studied.

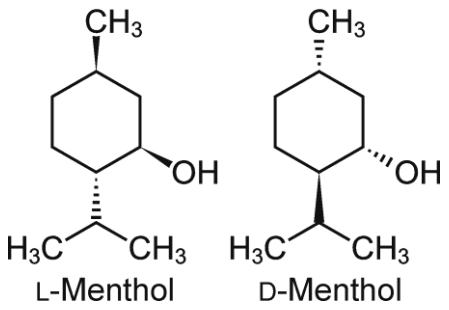

Figure 1. Molecular structures of L-menthol and D-menthol.

In this paper, the CLASSIC NMR strategy is applied to monitor crystallization of menthol (Figure 1) from the pure liquid (molten) phases of the racemic (DL-menthol) and enantiomerically pure (L-menthol) forms, with alternate measurement of $^{1}H \rightarrow ^{13}C$ ramp[12] cross-polarization[13] (CP) NMR spectra (giving signals only from solid phases) and direct-excitation ^{13}C NMR spectra (applied under conditions giving signals only from liquid phases) as a function of time during the experiment.

Menthol has widespread applications[14] based on its fragrance, flavour and cooling properties. These properties are associated primarily with the naturally occurring L-enantiomer.[15] It is now over 100 years since four polymorphic forms of L-menthol (denoted α, β, γ and δ) were first reported[16] to be distinguished by crystal habit, melting point and refractive index. The α polymorph is the most stable form and is the only polymorph with a known crystal structure[17] (although the unit cell of the β polymorph has been reported[18]). More recently, the β polymorph has been reported[18-19] to be obtained on quenching from the melt and the γ polymorph has been observed[20] in a flash differential scanning calorimetry (DSC) study.

An early structural study on DL-menthol suggested[21] that the most stable phase is a solid solution or "mixed crystal" of L-menthol and D-menthol, but this material was recently shown[18] to be a crystalline racemate with a regular ordered structure. The existence of two other forms (denoted PR1 and PR2) was also proposed,[18] where PR stands for pseudoracemate.[22] These materials are solid solutions of the two enantiomers, in which the end members of PR1 and PR2 correspond, respectively, to the α and β polymorphs of pure L-menthol. While PR2 has been isolated,[18] the less stable PR1 has only been observed[20] in a flash DSC experiment.

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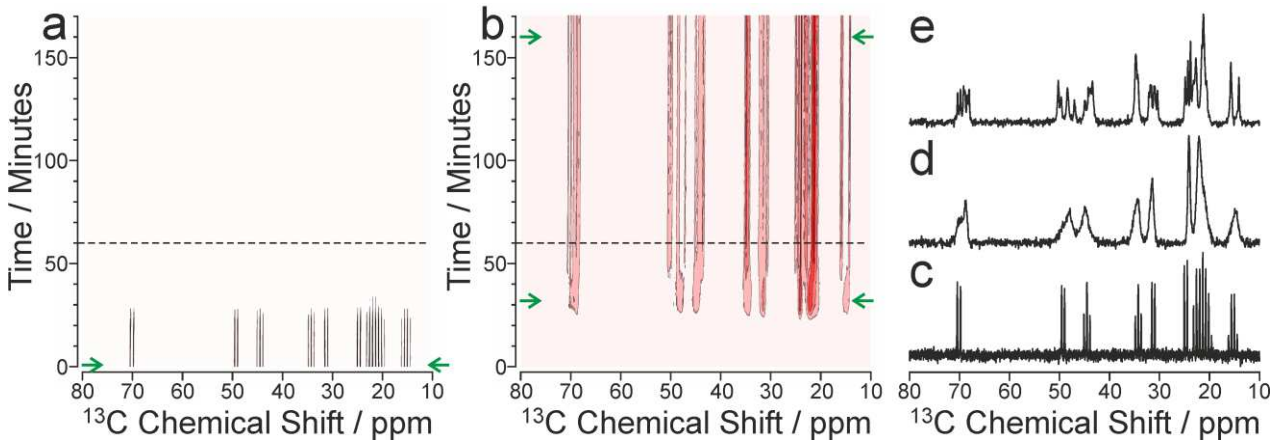


Figure 2. CLASSIC NMR data recorded as a function of time during slow cooling of DL-menthol from 35 °C to 15 °C (at –0.33 °C min^{-1}) and on leaving the sample at 15 °C for a further 110 min: (a) direct-excitation ^{13}C NMR spectra and (b) ^{1}H→^{13}C CP NMR spectra. Dashed lines indicate the end of the cooling process. Green arrows in (a) and (b) indicate the individual spectra shown in (c), (d) and (e). The first direct-excitation ^{13}C NMR spectrum acquired at the start of the experiment (35 °C) is shown in (c). ^{1}H→^{13}C CP NMR spectra recorded at starting times of 32 min and 160 min are shown in (d) and (e), respectively.

An aspect of crystallization of L-menthol and DL-menthol that has received virtually no attention[23] is the possibility that amorphous phases may be formed on the pathway to crystallization. Given the low melting points[18] of L-menthol (42.9 °C) and DL-menthol (33.8 °C), the molten phases are readily prepared and cooling under appropriate conditions may be anticipated to lead to glass formation. However, definitive evidence (from DSC data) for the formation of an amorphous phase of pure menthol has been reported[24] only for crystallization of menthol confined inside mesoporous silica host materials, with no evidence[24] for the formation of an amorphous phase in crystallization of L-menthol or DL-menthol from bulk (non-confined) molten phases, in agreement with previous literature.[23]

We first consider our CLASSIC NMR studies of crystallization of DL-menthol from the molten liquid, both under conditions of slow and fast cooling. In the slow cooling experiment, the sample was initially held at 35 °C to ensure melting, then cooled to 15 °C at –0.33 °C min^{-1}. Alternate ^{1}H→^{13}C CP NMR spectra and direct-excitation ^{13}C NMR spectra were recorded repeatedly, both during and after the cooling process (Figure 2). During the first 30 min, a signal was observed *only* in the direct-excitation ^{13}C NMR spectra (Figure 2a). The sharp peaks (J-coupled multiplets; Figure 2c) in this spectrum indicate that only liquid DL-menthol was present at this stage. At *ca*. 30 min ($T \approx 25$ °C), the signal in the direct-excitation ^{13}C NMR spectra due to the liquid phase disappears abruptly, while a signal appears concomitantly in the ^{1}H→^{13}C CP NMR spectrum (Figure 2b), indicating that rapid solidification of the entire liquid phase occurred at this time. At this stage, the ^{1}H→^{13}C CP NMR spectrum comprises only broad peaks (Figure 2d), consistent with an amorphous phase formed *via* a glass transition from the molten liquid phase.

The time-dependence of the ^{1}H→^{13}C CP NMR spectrum in the CLASSIC NMR experiment is shown in Figures 2b and 3. After *ca*. 45 min ($T \approx 20$ °C), the broad peaks due to the amorphous phase evolve over *ca*. 10 min into a set of much sharper peaks (Figure 2e) characteristic of a crystalline solid. This spectrum matches the solid-state ^{13}C NMR spectrum of the α polymorph of DL-menthol (Figure S1). Thus, our CLASSIC NMR data give clear evidence that an amorphous phase is formed initially upon solidification. After surviving for *ca*. 15 min, the amorphous phase transforms to the α polymorph of crystalline DL-menthol.

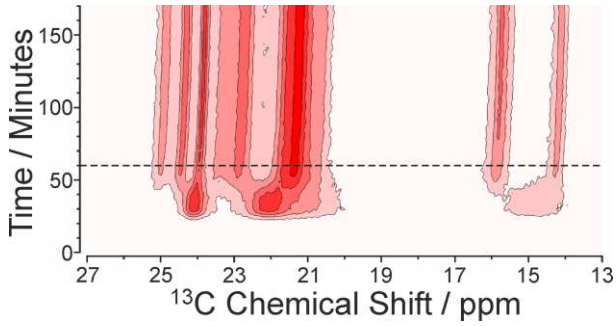


Figure 3. Expanded version (from 13 to 27 ppm) of the ^{1}H→^{13}C CP NMR spectra recorded during slow cooling of DL-menthol (same data as Figure 3b). The dashed line indicates the end of the cooling process.

CLASSIC NMR studies of crystallization of DL-menthol at faster cooling rates also reveal the transitory appearance of an amorphous phase. For example, when DL-menthol is cooled from 35 °C to 15 °C in less than 5 min (Figure 4), it is clear that an amorphous phase (characterized by broad peaks in the solid-state ^{13}C NMR spectrum; Figure 4b) was formed and persisted for a few minutes after the temperature reached 15 °C, before transforming to the crystalline α polymorph (Figure 4c).

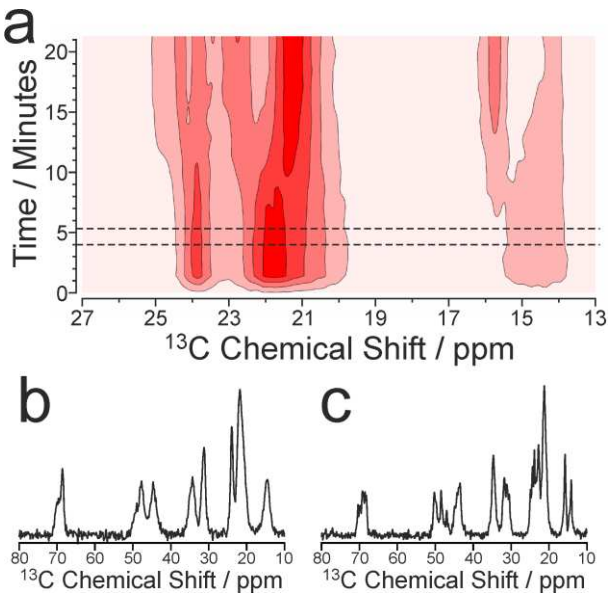


Figure 4. (a) $^{1}H \rightarrow ^{13}C$ CP NMR spectra recorded as a function of time during and after fast cooling of DL-menthol from 35 °C to 15 °C (the cooling process was complete after *ca.* 4 mins and the sample was maintained at 15 °C for the remainder of the experiment). Individual spectra recorded (b) between 4 min and 5 min 20 s and (c) between 20 min and 21 min 20 s. Dashed lines in (a) show the period during which the spectrum in (b) was recorded.

Our CLASSIC NMR studies of crystallization of L-menthol also involved separate experiments with fast and slow cooling. In fast cooling, the sample was held initially at 45 °C to ensure melting and then cooled to 15 °C over *ca.* 5 min (average cooling rate, 6 °C min^{-1}), with $^{1}H \rightarrow ^{13}C$ CP NMR spectra and direct-excitation ^{13}C NMR spectra recorded alternately as a function of time during and after the cooling process. No signal was detected in any of the direct-excitation ^{13}C NMR measurements, indicating that no liquid phase was present after the first 80 s of the cooling process (the time to record the first $^{1}H \rightarrow ^{13}C$ CP NMR spectrum), proving that the molten L-menthol solidified completely during this period. The time-dependence of the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum is shown in Figure 5. The first spectrum (recorded during the first 80 s of cooling; Figure 5a) has very broad peaks indicative of an amorphous phase, while the second spectrum (recorded towards the end of the cooling; Figure 5b) has much sharper peaks, characteristic of a crystalline phase. No significant changes are observed in the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum at subsequent times during the experiment. The solid-state ^{13}C NMR spectrum of the crystalline phase matches that of the α polymorph of L-menthol reported previously[25] (Figure S1).

In our CLASSIC NMR study of crystallization of L-menthol under slow cooling, the sample was held initially at 45 °C and then cooled to 15 °C at –0.36 °C min^{-1}. The time-evolution of the direct-excitation ^{13}C NMR spectra and $^{1}H \rightarrow ^{13}C$ CP NMR spectra are shown in Figure S2. For the first 25 min, a signal is observed only in the direct-excitation ^{13}C NMR spectrum (Figure S2a) indicating that only liquid L-menthol was present. After *ca.* 25 min ($T \approx 36$ °C), this signal disappears suddenly, while a signal appears at the same time in the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum (Figure S2b) indicating rapid solidification of the entire sample. However, in contrast to the results for DL-menthol (see above), the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum for L-menthol contains sharp peaks from the start of the solidification process, indicating the presence of crystalline material. Although the $^{1}H \rightarrow ^{13}C$ CP NMR spectra recorded just after solidification (Figure S2d) and at the end of the experiment (Figure S2e) are substantially similar, a discernible change in the spectrum occurs after *ca.* 60 min (see Figures S3 and S4), involving some increase in peak intensities and slight peak narrowing. At values of time significantly after the end of the cooling process, the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum (Figure S2e) matches the ^{13}C NMR spectrum of the α polymorph of L-menthol[25] (Figure S1).

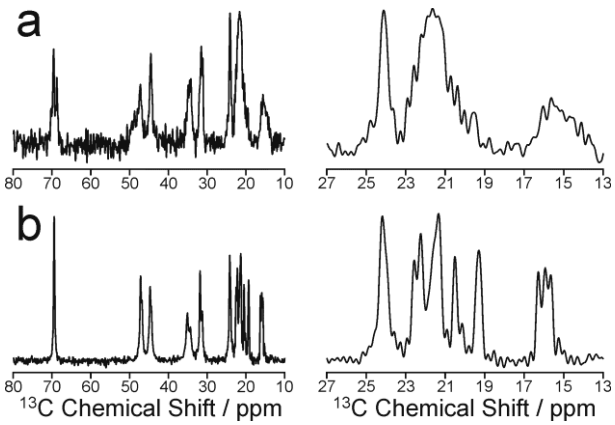


Figure 5. $^{1}H \rightarrow ^{13}C$ CP NMR spectra recorded during fast cooling of L-menthol from 45 °C to 15 °C in *ca.* 5 min: (a) spectrum recorded during the first 80 s and (b) spectrum recorded between 160 s and 240 s. In each case, both the full spectrum (left side) and the range from 13 to 27 ppm (right side) are shown.

The change in the $^{1}H \rightarrow ^{13}C$ CP NMR spectrum after *ca.* 60 min implies that two phases are initially present on solidification of the sample. While one phase is clearly identified as the α polymorph of L-menthol, identifying the second phase is more difficult. Given the polymorphic nature of L-menthol, it is possible that slow cooling initially produces a mixture of crystalline phases (the α polymorph and a second crystalline phase), which then evolves into a monophasic sample of the α polymorph by a polymorphic transformation. However, the change observed may also be consistent with initial formation of a mixture of crystalline (α polymorph) and amorphous phases, with the amorphous phase then transforming to the α polymorph over time.[26]

The results reported here demonstrate the significant potential of CLASSIC NMR to identify and characterize the transitory formation of amorphous phases on crystallization pathways, in addition to the well-proven ability of this technique to identify intermediate crystalline phases.[11c, 27] Our results constitute the first direct spectroscopic evidence that crystallization of DL-menthol and L-menthol from their molten phases can proceed *via* intermediate amorphous phases, emphasizing the importance of applying suitable *in-situ* experimental techniques to comprehensively monitor the time-evolution of crystallization processes. Similar *in-situ* solid-state NMR methodology may also be used to identify the formation of intermediate amorphous phases in solid-state chemical reactions.[28]

Finally, we consider the prospects for establishing structural details of the intermediate amorphous phases observed in our CLASSIC NMR studies of crystallization of L-menthol and DL-menthol from their molten liquid phases. The one-dimensional solid-state ^{13}C NMR spectra recorded in the CLASSIC NMR experiments reported here yield only very limited information about the structural properties of the amorphous phases, and more sophisticated NMR methods (for example, two-dimensional correlation experiments) would be significantly more informative in this regard. However, measurement of such spectra would require substantially longer time than the lifetimes of the transient amorphous phases observed during the evolution of the crystallization processes reported here, so it would be feasible to measure such spectra only if conditions could be found under which the kinetic stabilities (and hence the lifetimes) of the amorphous phases were increased.[29]

Given the transient nature of the amorphous phases, the best approach to gain insights into their structural properties would be to apply other *in-situ* experimental methods that are able to provide detailed structural information on amorphous phases and for which rapid measurement of data under *in-situ* conditions is possible. The most promising strategy would be to record *in-situ* X-ray scattering data, followed by pair-distribution function (PDF) analysis[30] of the data for the transient amorphous phases.[31]

Clearly, for other systems in which intermediate amorphous phases are formed on the pathway towards crystallization and with significantly longer lifetimes than those observed here for L-menthol and DL-menthol, a combined approach involving both CLASSIC NMR studies (using two-dimensional correlation experiments to record the solid-state NMR data) and PDF analysis of *in-situ* X-ray scattering data would represent a very powerful strategy for structural characterization of the intermediate amorphous phases.

Experimental Section

Powder samples of L-menthol and DL-menthol were used as purchased from Alfa Aesar and were confirmed by powder XRD to be the α polymorph[17-18] in each case. High-resolution solid-state ^{13}C NMR spectra for each material are shown in Figure S1. For the CLASSIC NMR experiments, the samples were sealed inside 4 mm rotors (internal diameter 2.98 mm) and subjected to MAS at 12 kHz. DL-Menthol was melted by heating to 35 °C and L-menthol was melted by heating to 45 °C. The molten liquids were either cooled slowly (using a gradually decreasing set temperature) or quickly (by immediately reducing the set temperature to the final target temperature).[32] Determination of temperature was based on a calibration using lead nitrate[33] and verified in the temperature range of our experiments by measurements on methanol.[34] These calibrations took into consideration the heating effect due to MAS. The accuracy of the temperature measurement is estimated to be within ±1 K. More detailed descriptions of the measurement techniques used in the CLASSIC NMR experiments are given in SI.

Acknowledgements

We are grateful to Cardiff University for financial support and the UK High-Field Solid-State NMR Facility for spectrometer time. This facility was funded by EPSRC, BBSRC and the University of Warwick, including part funding through Birmingham Science City Advanced Materials Projects 1 and 2 supported by Advantage West Midlands and European Regional Development Fund. We thank Dr Dinu Iuga for experimental assistance and Prof. Hugo Christenson for discussions.

Keywords: Amorphous Phases • Solid-State NMR • Crystallization • *In Situ* Studies • Menthol

[1] (a) D. Gebauer, M. Kellermeier, J. D. Gale, L. Bergström, H. Cölfen, *Chem. Soc. Rev.* **2014**, *43*, 2348-2371; (b) M. Descamps, E. Dudognon, *J. Pharm. Sci.* **2014**, *102*, 2615-2628.

[2] S. Weiner, L. Addadi, *Annu. Rev. Mater. Res.* **2011**, *41*, 21-40.

[3] (a) J. D. Rodriguez-Blanco, S. Shaw, L. G. Benning, *Nanoscale* **2011**, *3*, 265-271; (b) J. Ihli, W. C. Wong, E. H. Noel, Y.-Y. Kim, A. N. Kulak, H. K. Christenson, M. J. Duer, F. C. Meldrum, *Nature Commun.* **2014**, *5*, 3169.

[4] P. A. Williams, C. E. Hughes, K. D. M. Harris, *Cryst. Growth Des.* **2012**, *12*, 5839-5845.

[5] Y. N. Thi, K. Rademann, F. Emmerling, *CrystEngComm* **2015**, *17*, 9029-9036.

[6] (a) D. Gebauer, H. Cölfen, *Nano Today* **2011**, *6*, 564-584; (b) D. Erdemir, A. Y. Lee, A. S. Myerson, *Acc. Chem. Res.* **2009**, *42*, 621-629; (c) R. J. Davey, S. L. M. Schroeder, J. H. ter Horst, *Angew. Chem. Int. Ed.* **2013**, *52*, 2166-2179; (d) J. J. De Yoreo, P. U. P. A. Gilbert, N. A. J. M. Sommerdijk, R. L. Penn, S. Whitelam, D. Joester, H. Zhang, J. D. Rimer, A. Navrotsky, J. F. Banfield, A. F. Wallace, F. M. Michel, F. C. Meldrum, H. Cölfen, P. M. Dove, *Science* **2015**, *349*, aaa6760; (e) D. Zahn, *ChemPhysChem* **2015**, *16*, 2069-2075; (f) *Nucleation – A Transition State to the Directed Assembly of Materials, Faraday Discussions, Vol. 179*, RSC Publishing, **2015**.

[7] N. Pienack, W. Bensch, *Angew. Chem. Int. Ed.* **2011**, *50*, 2014-2034.

[8] R. K. Harris, *Analyst* **2006**, *131*, 351-373.

[9] M. Skotnicki, D. C. Apperley, J. A. Aguilar, B. Milanowski, M. Pyda, P. Hodgkinson, *Mol. Pharmaceutics* **2016**, *13*, 211-222.

[10] C. E. Hughes, P. A. Williams, K. D. M. Harris, *Angew. Chem. Int. Ed.* **2014**, *53*, 8939-8943.

[11] (a) C. E. Hughes, K. D. M. Harris, *J. Phys. Chem. A* **2008**, *112*, 6808-6810; (b) C. E. Hughes, K. D. M. Harris, *Chem. Commun.* **2010**, *46*, 4982-4984; (c) C. E. Hughes, P. A. Williams, T. R. Peskett, K. D. M. Harris, *J. Phys. Chem. Lett.* **2012**, *3*, 3176-3181; (d) V. S. Mandala, S. J. Loewus, M. A. Mehta, *J. Phys. Chem. Lett.* **2014**, *5*, 3340-3344; (e) K. D. M. Harris, C. E. Hughes, P. A. Williams, *Solid State Nucl. Magn. Reson.* **2015**, *65*, 107-113; (f) C. E. Hughes, P. A. Williams, V. L. Keast, V. G. Charalampopoulos, G. R. Edwards-Gau, K. D. M. Harris, *Faraday Discuss.* **2015**, *179*, 115-140; (g) K. D. M. Harris, C. E. Hughes, P. A. Williams, G. R. Edwards-Gau, *Acta Crystallogr. Sect. C: Struct. Chem.* **2017**, *73*, 137-148.

[12] G. Metz, X. L. Wu, S. O. Smith, *J. Magn. Reson. A* **1994**, *110*, 219-227.

[13] S. R. Hartmann, E. L. Hahn, *Phys. Rev.* **1962**, *128*, 2042-2053.

[14] R. Eccles, *J. Pharm. Pharm. Sci.* **1994**, *46*, 618-630.

[15] G. Ohloff, *Scent and Fragrances*, Springer-Verlag, Heidelberg, **1994**.

[16] F. E. Wright, *J. Am. Chem. Soc.* **1917**, *39*, 1515-1524.

[17] P. Bombicz, J. Buschmann, P. Luger, N. X. Dung, C. B. Nam, *Z. Kristallogr.* **1999**, *214*, 420-423.

[18] Y. Corvis, P. Négrier, S. Massip, J.-M. Léger, P. Espeau, *CrystEngComm* **2012**, *14*, 7055-7064.

[19] Y. Corvis, P. Négrier, M. Lazerges, S. Massip, J.-M. Léger, P. Espeau, *J. Phys. Chem. B* **2010**, *114*, 5420-5426.

[20] Y. Corvis, A. Wurm, C. Schick, P. Espeau, *CrystEngComm* **2015**, *17*, 5357-5359.

[21] M. Kuhnert-Brandstätter, R. Ulmer, L. Langhammer, *Arch. Pharm.* **1974**, *307*, 497-503.

[22] (a) F. S. Kipping, W. J. Pope, *J. Chem. Soc. Trans.* **1897**, *71*, 989-1001; (b) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, John Wiley & Sons, New York, **1981**.

[23] In a flash DSC study (reference 18), a feature observed in the DSC data on heating a sample of L-menthol that had been rapidly quenched was interpreted as a glass transition.

[24] T. Cordeiro, C. Castiñeira, D. Mendes, F. Danède, J. Sotomayor, I. M. Fonseca, M. Gomes da Silva, A. Paiva, S. Barreiros, M. M. Cardoso, M. T. Viciosa, N. T. Correia, M. Dionisi, *Mol. Pharmaceutics* **2017**, *14*, 3164-3177.

[25] R. Sangill, N. Rastrup-Andersen, H. Bildsøe, H. J. Jakobsen, N. C. Nielsen, *J. Magn. Reson. A* **1994**, *107*, 67-78.

[26] We note that the regions with greater peak broadening in the solid-state ^{13}C NMR spectrum (Figure S4a) of the material produced initially on solidification in the slow cooling of L-menthol (from *ca*. 13 to 17 ppm and from ca. 20 to 23 ppm) correspond to the spectral regions in which the amorphous phase observed in the fast cooling of L-menthol gives rise to broad peaks.

[27] A relevant question is whether the crystallization pathways observed in CLASSIC NMR studies may be influenced by the fact that the NMR measurement technique requires that the sample is subjected to rapid uniaxial rotation (MAS) which generates a pressure in the sample that increases radially within the cylindrical rotor from zero on the rotation axis to *ca*. 64 atm at the walls of the rotor (for an MAS frequency of 12 kHz). To probe this issue, CLASSIC NMR experiments were also carried out at significantly lower MAS frequency of 2 kHz (which generates a pressure of *ca*. 1.8 atm at the walls of the rotor) and were observed to give the same behaviour, suggesting that crystallization of DL-menthol and L-menthol from their molten phases is not influenced by pressure effects due to MAS (such pressure effects are discussed in reference 11f).

[28] D. de Loera, A. Stopin, M. A. Garcia-Garibay, *J. Am. Chem. Soc*. **2013**, *135*, 6626-6632.

[29] Our CLASSIC NMR experiments on L-menthol and DL-menthol explored a range of different cooling schedules, including experiments in which the cooling process was stopped at different temperatures, but we were unable to find conditions under which the amorphous phases survived for significantly longer periods of time.

[30] (a) S. J. L. Billinge, M. G. Kanatzidis, *Chem. Commun*. **2004**, 749-760; (b) R. B. Neder, V. I. Korsunskiy, *J. Phys.: Condens. Matter* **2005**, *17*, S125-S134; (c) M. W. Terban, E. Y. Cheung, P. Krolikowski, S. J. L. Billinge, *Cryst. Growth Des*. **2016**, *16*, 210-220.

[31] If sufficiently detailed structural information on the amorphous phases could be gained from PDF analysis, it may be feasible to unravel mechanistic aspects of the transformations from the amorphous phases to the crystalline phases using appropriate computer simulation techniques.

[32] We note that, as the temperature of the magnetic shims decreases during the experiment, the applied magnetic field changes slightly (and in a monotonic manner) with time. As a result, the measured chemical shifts exhibit a slight monotonic drift as a function of time. As we do not carry out any quantitative analysis of the measured chemical shifts in the present paper, they have not been corrected to compensate for this slight monotonic drift, but such corrections can be applied to the data as discussed previously (see reference 10).

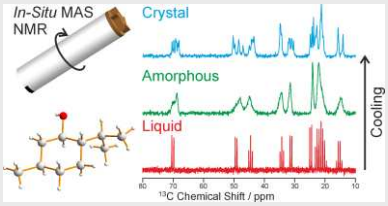
[33] A. Bielecki, D. P. Burum, *J. Magn. Reson. A* **1995**, *116*, 215-220.

[34] (a) A. L. Van Geet, *Anal. Chem*. **1968**, *40*, 2227-2229; (b) A. L. Van Geet, *Anal. Chem*. **1970**, *42*, 679-680; (c) A. E. Aliev, K. D. M. Harris, *Magn. Reson. Chem*. **1994**, *32*, 366-369.

Entry for the Table of Contents

COMMUNICATION

Crystallization *via* amorphous intermediates: Application of the CLASSIC NMR technique for *in-situ* studies of crystallization of L-menthol and DL-menthol from their molten phases reveals direct spectroscopic evidence for the transient existence of amorphous phases prior to crystallization. The CLASSIC NMR strategy allows the time-evolution of the liquid, amorphous and crystalline phases to be studied simultaneously in the same crystallization experiment.



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